Clinical utility trial incorporating biomarkers into a risk model for lung cancer screening

S. Hanash
20 Year Journey

What have we done
20 Year Journey

What have we done
Where are we at
20 Year Journey

What have we done
Where are we at
Where do we go from here
Disclosures

- IP/Invention disclosures filed for pan-cancer, lung cancer, pancreatic cancer, colon cancer, ovarian cancer and prostate cancer biomarkers and for therapeutic targets
- *IP licensed to Thrive (now Exact Sciences), Dynex, Cosmos, OnclImmune*
- Consultant to: Abbott, Abbvie, BMS, Takeda
Why a utility trial for lung cancer

• #1 cancer killer
• Smokers are at increased risk for other diseases, cancers
• A utility trial for lung cancer provides an opportunity for validation of pan-cancer markers
Lung cancer screening recommendations

• Current USPSTF: Annual low-dose CT for smokers with at least 30 pack-years and no more than 15 years since quitting, ages 55-80 (CMS: ages 55-77, shared-decision making)

• New 2020 USPSTF draft recommendations: reduce pack-years to 20 and age to 50, quit < 15 years

• Still leave out a good percentage of subjects destined to be diagnosed with lung cancer
Potential benefits of personalized risk assessment

• Bring to screening subjects that don’t meet eligibility criteria but have a personalized risk equivalent to risk for eligible subjects so as to catch more lung cancers early
• Reduce screening needs for subjects that meet eligibility criteria but have a reduced personalized risk
• Contribute to assessment of indeterminate nodules
• Increase uptake of CT screening
An immune response manifested by the common occurrence of annexins I and II autoantibodies and high circulating levels of IL-6 in lung cancer

Franck M. Brichory, David E. Misek, Anne-Marie Yim, Melissa C. Krause, Thomas J. Giordano, David G. Beer, and Samir M. Hanash

PNAS August 14, 2001 98 (17) 9824-9829; https://doi.org/10.1073/pnas.171320598

> 70 papers to date
Discovery and validation of ProSFTPB as anchor marker for early detection of lung cancer

- Discovery based on proteomics applied to animal models of lung cancer and subjects with early stage lung cancer led to the discovery of ProSFTPB (Cancer Cell 2011)
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- Validation of ProSFTPB in pre-diagnostic samples from the CARET and PanCan cohorts (JCO 2013) and the Harvard PHS cohort (CEBP 2013)
Discovery and validation of ProSFTPB as anchor marker for early detection of lung cancer

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- Validation of ProSFTPB in pre-diagnostic samples from the CARET and PanCan cohorts (JCO 2013) and the Harvard PHS cohort (CEBP 2013)
- Validation of the combination of ProSFTPB + DAS in CARET cohort (JCO 2015)
Pro-Surfactant Protein B Identifies Incident Lung Cancers

- Abnormal CT-No LC: N=819
- LC-Incidence: N=17
- LC-Prevalence: N=107
- Normal-No LC: N=1544

P < 0.01
P = 0.027
P < 0.01
Road map

- > 10,000 lung cancer biomarker papers
- Pick out initial marker type(s)/platform(s)
- Consider analytical variability, practicality, cost effectiveness of biomarker combinations
Search for biomarkers with potential utility for lung cancer screening

- Nucleic acids:
  - Mutated DNA
  - Non-coding RNA
- Metabolites
- Immune related:
  - Cytokines/chemokines
  - Autoantibodies
- Circulating microparticles/exosomes
MD Anderson miRNA candidate list

- 74 with at least one publication for early detection
- 20 with at least two publications for early detection (+)
- 25 (‡) consistently over-expressed in IPAS (across 42 Lung Cancer cell lines), including 7 with more than 1 Early Detection publication, 12 with only 1 Early Detection publication (‡), and 6 not related to Early Detection (‡)
- 8/25 consistently over-expressed in IPAS LC cell lines also in Sozzi’s list

Other considerations:
- Overlap miRNAs across three independent review analyses (10 miRNAs)
- Sozzi’s miRNAs (24 miRNAs) (•)
- Rosetta Genomics miRNAs for tumor differentiation (†)

miR-21•‡†+, miR-210+, miR-205†, miR-145•+, miR-182, miR-101•, miR-375†, miR-31‡, miR-203, miR-16•, miR-17•‡+, miR-486-5p•+, miR-126•+, miR-140-5p•+, miR142-3p•+, miR-148a•+, miR-30b•‡+, miR-30c•‡+, miR-92a•‡+, miR106a•‡†, miR-133a•, miR-140-3p•, miR-15b•‡+, miR-197•, miR-19b•, miR-221•‡+, miR-28-3p•+, miR-320•+, miR-451•+, miR-660•+, miR-125a-5p†‡, miR-129-3p†, miR-29b†, miR-7† (34 miRNAs)

Potential Additional miRNAs:
Let-7a†, mir-20a‡, mir-24‡, mir-29a‡, let-7b‡, mir-103‡, mir-222‡, mir-30a‡, mir-139-5p‡, mir-26a‡, mir-27b‡, mir-125b‡, let-7f†, mir-34a†, mir-23a‡
Additional relevant proteins that could be added with no sample volume “cost” due to their presence in commercial panels

- **Singleplex or other panel (not related to each other)**
- **In-house**
- **HCCBP1MAG-58K**
- **Millipore 2**
- **HCYTMAG-60K**
- **R&D screen**
- **Bio-Rad LZ0000D2DTE31D**
- **Bio-Rad LH000001VR**
- **HKI5MAG-99K**
- **HBNMAG-62K**
Example of performance of markers from more than one platform based on pre-diagnostic CARET Cohort
• Extensive validation of ProSFTPB justified considering ProSFTPB as anchor marker for lung cancer screening
• A total of an additional 50 marker candidates were tested in the CARET cohort that resulted in a 4-marker panel (4MP = ProSFTPB, CEA, CA125, CYFRA21)
• 4MP validated in the European Northern Sweden and EPIC Cohorts (Guida et al JAMA Oncol 2018)
ROC curve analysis in the validation study (EPIC and NSHDS ever smoker subjects diagnosed within 1 year of blood collection) for two risk prediction models, smoking variables only, and an integrated model with the smoking variables and the biomarker score combined.
PLCO validation study

Based on combination of:

4-protein marker panel (4MP)

+ Lung cancer risk model (PLCO 2012)
  (Tammemagi M etal NEJM 2013)
PLCO Validation Study

- Ziding Feng and Tracey Marsh *Fred Hutch*
- Martin Tammemagi *Brock University*
- Stephen Lam *UBC*
- Rafael Meza *U of Michigan*
- Margaret Spitz *Baylor*
- Sanjay Shete *MDA*
You did not list Tracey!
PLCO Cohort Validation Study

- Ed Ostrin
- Johannes Fahrmann
- Ehsan Irajizad
- Jody Vykokal
- Jennifer Dennison
- Nikul Patel
**PLCO Cohort**

<table>
<thead>
<tr>
<th>Total samples tested</th>
<th># of cases (within 5 years of time to DX)</th>
<th># of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>10605</td>
<td>1299</td>
<td>8746</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to DX: [0-1)</th>
<th>All cases</th>
<th>Adenocarcinoma</th>
<th>Squamous</th>
<th>Small cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>370</td>
<td>152</td>
<td>82</td>
<td>51</td>
</tr>
</tbody>
</table>

**Markers Tested:**
ProSFTPB, CEA, CA125, CYFRA21
**Development of decision rule based on 4MP+PLCO 2012**

**Blinded training set with fixed 4MP combination rule**

<table>
<thead>
<tr>
<th>Total samples tested</th>
<th>Number of Cases</th>
<th>Number of Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>4554</td>
<td>538</td>
<td>3764</td>
</tr>
</tbody>
</table>

**Time to DX: [0-1) : # of Cases: 152 # of Controls: 3764**

**Blinded Validation with decision rule**

<table>
<thead>
<tr>
<th>Total samples tested</th>
<th>Number of Cases</th>
<th>Number of Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>6051</td>
<td>761</td>
<td>4945</td>
</tr>
</tbody>
</table>

**Time to DX: [0-1) : # of Cases: 218 # of Controls: 4945**
Training

Validation
PLCO Cohort – 4MP + PLCOm2012

Training

Validation
**Lung risk groups based on smoking criteria**

( + = eligible based on USPSTF criteria)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Analysis</th>
<th>TF2013</th>
<th>TF2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10py</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10-20py</td>
<td>Low</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20-29py;≥15qy</td>
<td>Low</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20-29py;&lt;15qy</td>
<td>Med</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>30+py;≥15qy</td>
<td>Med</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>30+py;&lt;15qy</td>
<td>High</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**USPSTF Criteria: Current (TF2013) and recent draft (TF2020)**
### 4MP + PLCOm2012 (1% risk)

<table>
<thead>
<tr>
<th>strata</th>
<th>AUC</th>
<th>sens</th>
<th>spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.794</td>
<td>0.500</td>
<td>0.906</td>
<td>0.029</td>
<td>0.997</td>
</tr>
<tr>
<td>Med</td>
<td>0.778</td>
<td>0.682</td>
<td>0.611</td>
<td>0.033</td>
<td>0.990</td>
</tr>
<tr>
<td>High</td>
<td>0.817</td>
<td>0.986</td>
<td>0.269</td>
<td>0.047</td>
<td>0.998</td>
</tr>
<tr>
<td>All</td>
<td>0.842</td>
<td>0.884</td>
<td>0.562</td>
<td>0.043</td>
<td>0.995</td>
</tr>
</tbody>
</table>
The 0.01% should be 1%, the 6-yr risk of 1.0%.

Feng PhD, Ziding, 10/24/2020
### 4MP + PLCOm2012 (1.7% risk)

<table>
<thead>
<tr>
<th>strata</th>
<th>AUC</th>
<th>sens</th>
<th>spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.794</td>
<td>0.438</td>
<td>0.956</td>
<td>0.053</td>
<td>0.997</td>
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<tr>
<td>Med</td>
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<td>0.614</td>
<td>0.775</td>
<td>0.051</td>
<td>0.990</td>
</tr>
<tr>
<td>High</td>
<td>0.817</td>
<td>0.944</td>
<td>0.445</td>
<td>0.058</td>
<td>0.995</td>
</tr>
<tr>
<td>All</td>
<td>0.842</td>
<td>0.835</td>
<td>0.693</td>
<td>0.057</td>
<td>0.995</td>
</tr>
</tbody>
</table>
again should be 0.017, not 0.017%
Feng PhD, Ziding, 10/24/2020
4MP+PLCOM2012 vs TF
Clinical utility trial incorporating biomarkers into a risk model for lung cancer screening

- **Trial concept**: An intervention trial to compare sensitivity and specificity of biomarker driven decision rule vs that of TF2020 guideline
- **Hypothesis**: A risk model driven intervention (at threshold of 6-yr risk 1.0%) will have higher sensitivity (sensitivity at 12m follow up) and better specificity than that by TF2020
- **Study outcome**: Lung cancer within 12 m of enrollment
- **Study endpoint**: comparison of sensitivity and specificity of risk model vs TF2020
Clinical utility trial incorporating biomarkers into a risk model for lung cancer screening

Eligibility:

• 10+ py smokers currently not eligible but that meet a 6 y risk threshold of 1% based on 4MP + PLCO 2012 will undergo LDCT N= 14,000

• Most currently eligible subjects do not undergo LDCT screening. Currently eligible subjects undecided re LDCT will be informed of their risk based on 4MP + PLCO 2012 will be informed of their risk through shared decision making N=7,000

• Currently eligible subjects that undergo LDCT N=7,000 (MDACC Leap Study already recruited > 8,000 subjects in this group)
Study requirements

- Baseline + one year blood collection
- Baseline + one year LDCT (for current risk group)
- Follow-up: three years from baseline
- Management of positive subjects according to current guidelines
FPZ2  Red text means that they are not required to answer the primary hypothesis of the trial, thus they are optional for debate
Feng PhD, Ziding, 10/24/2020
Secondary objectives

- Screening uptake rate (proportion of guideline eligible who did not plan to take screening LDCT at baseline who ended up taking screening LDCT within 12m from baseline)
- Contribution of subject risk + nodule characteristics to assessment of indeterminate nodules *(Ostrin E et al JTO in press)*
- Biospecimen repository for testing other promising markers for lung cancer or for pan-cancer
Power calculations

- Model sensitivity 88% vs TF2020 sensitivity 80%
- Model specificity 58% vs TF2020 specificity 51%
- 28,000 enrolled, 90% power
- Distribution of enrolled represents the distribution of 10+ PY smokers in US (~50% eligible, ~50% ineligible)
- 8,000 enrolled in Leap Study potentially relevant
LEAP Participating Sites

- MD Anderson – Houston, TX
- US Cancer Network Sites (AL, FL, OH, NJ, TX)
- USC
- Stanford
- Sister Institutions in Europe (Madrid, Paris)
- Sister Institutions in China (Anhui, Henan, Xuzhou)

Site Visits
LDCT, Blood, Questionnaire

Y0 Y1
LEAP – US & European Sites
Total Number of Visits

5706 blood specimens (280,000 aliquots)
50 lung cancers, 55 other cancers
Why not present # from China?
Feng PhD, Ziding, 10/24/2020
Acknowledgements

• **Lab group:** Mitzi Aguilar, Clemente Aguilar, Frank Brichory, Michela Capello, Julian Casabar, Muge Celiktas, Juan Chen, Jennifer Dennison, Dilsher Dhillon, Corinthia Emery, Johannes Fahrmann, Hiroyuki Katayama, Makoto Kobayashi, Deepali Kundnani, Jon Ladd, Vivuen liu, Amin Momin, Eunice Murage, Nikul Patel, Nan Sun, Ayumu Taguchi, Saty Tripathi, Peiling Tsou, Nese Unver, Jody Vykokal, Hong Wang, Peng Wang, Hanasen, Xu, B. Yang, Chuan-Yih Yu.

FUNDING SUPPORT

CARET : NCI EDRN, DOD LRCP
WHI : NHLBI BAA
PHS : NCI R21
EPIC : NCI U01
PLCO : NCI U01, NCI SCLC Consortium

Foundations: Canary, Lungevity, Rubenstein Family, Houston Cancer Fighters, Lyda Hill
Discussion items

• Should we have a non-intervention control arm?
• Is year one LDCT a requirement or subject follow-up is enough?
• Merits of expanding trial to outside US eg Canada, Europe, China and Australia?
Launch of ACED

Association for Cancer Early Detection